Journal of Basic and Clinical Pharmacy

www.jbclinpharm.com

DEVELOPMENT OF NOVEL, ALTERNATIVE, FACILE, ECOFRIENDLY, HIGH YIELD SYNTHETIC PROCESS FOR PRAZOSIN

D. A. Patil[1]*, K. S. Jain[2], M. N. Deodhar[3], P. O. Patil[1], G. B. Patil[1] and D. D. Patil[1]

[1]Department of Pharmaceutical Chemistry, H. R. Patel Institute of Pharmaceutical Education and Research, Karwand Naka, Shirpur - 425 405, Dhule, Maharashtra, India
[2]Department of Pharmaceutical Chemistry, Sinhgad College of Pharmacy, Vadgaon (Bk), Pune - 411 041, India
[3]Department of Pharmaceutical Chemistry, S.G.R.S. College of Pharmacy, Saswad, Pune - 411 025, India

ABSTRACT: Industrial chemistry in the new millennium is widely adopting the concept of "*Green chemistry*" to meet the fundamental scientific challenges. Antihypertensive drugs include several of the most widely prescribed drugs like diuretics, beta-blockers, ACE inhibitors, calcium channel blockers, and α-1 adrenoreceptor blockers. The discovery of prazosin, with very high index of α_1/α_2 affinity has triggered off a renaissance of interest in α_1-adrenoceptor antagonist drugs for treatment of hypertension. The three reported routes for synthesis and manufacture of the α-adrenoceptor antagonist- prazosin had some disadvantages. In present study we had developed new methods for the synthesis of prazosin by using microwave. The most important aspect is the overall yield of this process was ~25 % higher than the other reported methods excluding the use of banned substances.

KEYWORDS: prazosin, green chemistry, process development.

received on 26-03-2010
modified on 28-09-2010
accepted on 28-10-2010
available online 15-11-2010
www.jbclinpharm.com

INTRODUCTION

Diseases of the arterial tree caused more premature deaths than all other diseases such as cancer and infections combined. Among the major risk factors for arterial diseases, high blood pressure has been identified as the most powerful one [1]. Lowering blood pressure in hypertensive patients requires not only a broad choice of effective and well tolerated medications, but also skills to motivate them to comply with the lifelong treatment.

Antihypertensive drugs include several of the most widely prescribed drugs like diuretics, beta-blockers, ACE inhibitors, calcium channel blockers, and α-1 adrenoreceptor blockers. These drugs are also used for other indications including heart failure, ischemic heart disease and renal disease. The most widely used antihypertensive drugs fall into six mechanistic "classes". To treat hypertension more than 100 chemical entities are marketed internationally. The number of patients existing for every class of antihypertensive drugs is nearly hundreds and thousands of individual chemical entities are identified to treat hypertension.

Prazosin (a) and its analogs, Fig. (1), or congener drugs namely, Terazosin (b), Doxazosin (c), Alfuzosin (d), Bunazosin (e), and Quinazosin (f) have achieved significant usage as selective α1-adrenoreceptor antagonist drugs useful for the treatment of 'primary' or 'essential hypertension,' the most common of the cardiovascular disease of modern times and which accounts for nearly 40% of the deaths worldwide [2, 3].

As the logical approach for effective management of the arterial hypertension, prazosin and its analogs, with a strong vasodilatory action on the arteriolar vascular bed are used widely. They had many advantages like dictating both resistance and capacitance of blood vessels, favorable haemodynamic effects, virtual absence of reflux tachycardia, maintenance of renal blood flow and glomerular filtration rate and intact auto regulation of noradrenaline due to non-blockade

*Corresponding Author:
Email: dilipapatil@gmail.com

of presynaptic α_2-adrenoceptors. They also had favorable effect on lipid profile, carbohydrate metabolism and insulin resistance. These drugs are also useful in the treatment of congestive heart disease (CHD), variant or prinzmetal's angina, raynaud's disease etc. However, there is a need of developing more specific

Figure 1: Structure of Lead Molecules (Prazosin (a), Terazosin (b), Doxazosin (c), Alfuzosin (d), Bunazosin (e), Quinazosin (f)).

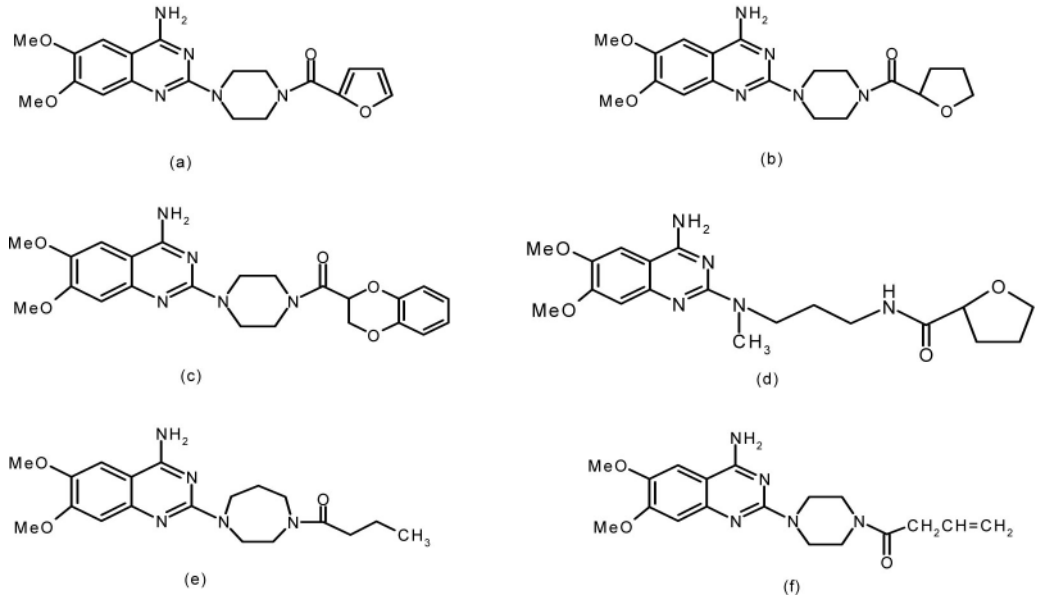
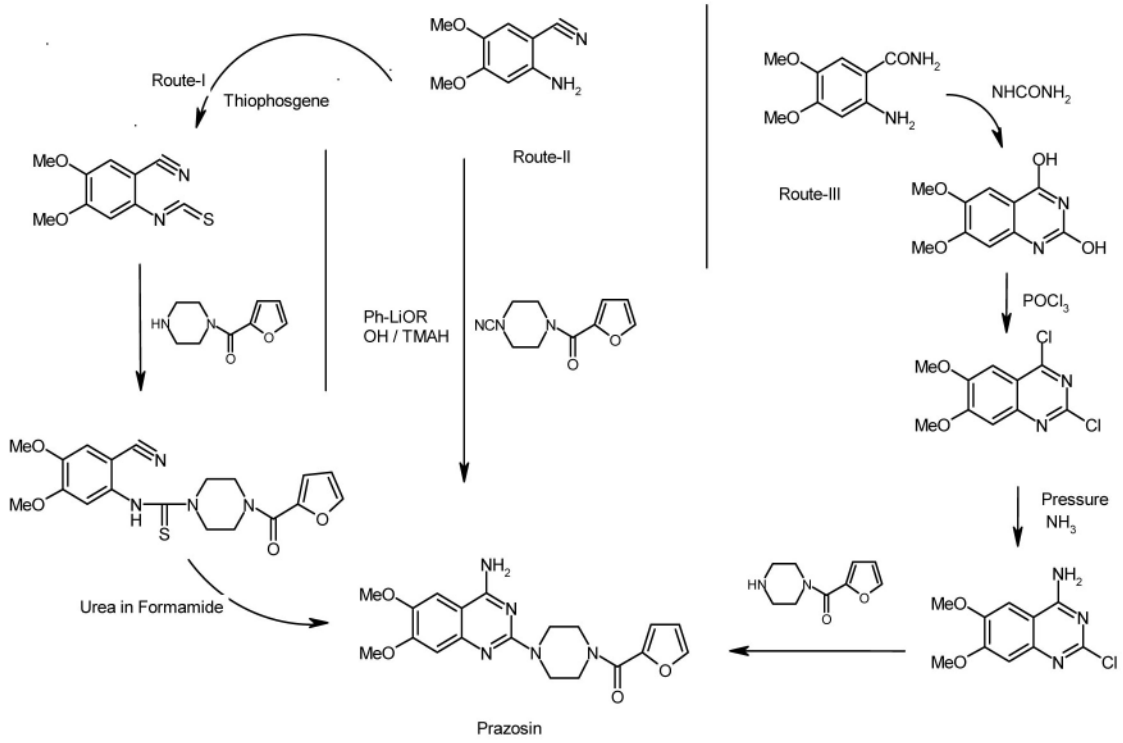


Figure 2: Reported routes for synthesis of Prazosin



analogs with specific affinities to α_1-adrenoceptor subtypes to remove their side effects [3].

Prazosin has achieved significant clinical usage in the country and has been included in the Indian Pharmacopoeia 1996. However, there are very few Indian manufacturers of prazosin (only one), terazosin (two) and doxazosin (three), which include all Hyderabad based companies namely, Dr. Reddy's holding (Trident), Aurobindo Pharma, Heterodrugs and SMS Pharmaceuticals. No Indian manufacturer for Bunazosin, Trimazosin and Alfuzosin is listed. A large number of Indian formulators import these drugs. The currently used processes[4,5] for prazosin analogs suffered from many drawbacks like low yields, use of thiophosgene, drastic reaction conditions, high Raw Material Cost (RMC) etc. The reported routes for the synthesis and manufacture as depicted below had some disadvantages like Fig. (2);

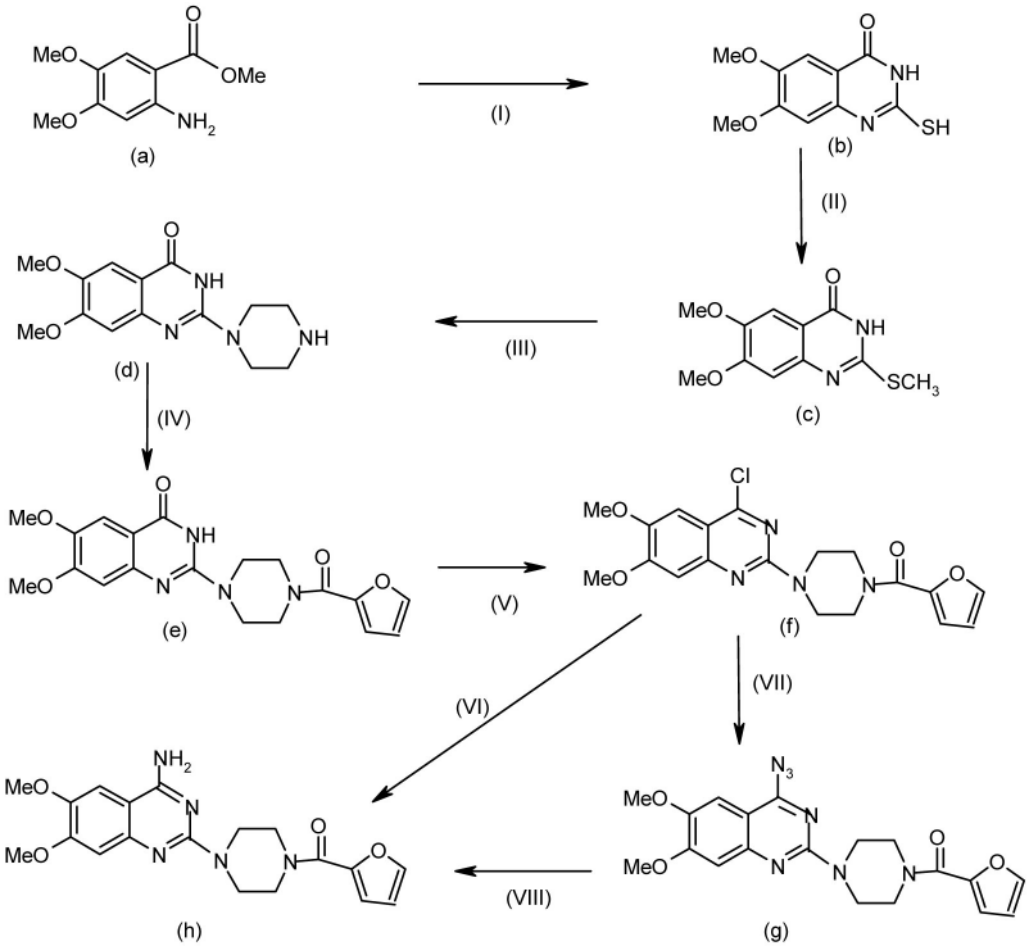
Route I: Overall yields 8-10%, use of Thiophosgene (toxic and banned substance which had carcinogenic property).

Route II: Very low overall yields, drastic reaction conditions and prolonged reaction time required to complete the reactions.

Route III: Longer synthesis of multiple steps, which increased the overall cost of the product.

There was a need and opportunity to develop an alternative, cost effective, facile and eco-friendly route for the synthesis of prazosin and its congeners.

Figure 3: (I) $NH\neg\neg\neg\neg_2CSNH_2$, HCL(50%), MW; (II) dimethyl sulphate, NaOH (20%), 0-5°C, 3-4h; (III) unhydrous piperazine, isopropyl alcohol, MW; (IV) 2-furoyl chloride, isopropyl alcohol, potassium carbonate, TEBA chloride, MW; (V) $POCl_3$, isopropyl alcohol, MW; (VI) NH_3, THF, 0-5°C, 2h; (VII) NaN_3, THF, 145-150°C; (VIII) Zn, AcOH, 85-90°C.



MATERIALS AND METHODS

Source of chemicals and apparatus

Reagents used in the synthesis were of analytical or laboratory grade and were used as supplied or were prepared according to procedures described in literature. Solvents except analytical reagent grade were dried and purified according to literature when necessary. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel F254 plates from Merck and compounds visualized by exposure to UV light. Melting points were determined in open capillary with Veego electronic apparatus and are uncorrected.

The IR spectra were recorded using potassium bromide on JASCO V-5300 FT-IR. The ^{1}H NMR spectra were recorded in $CDCl_3$ and DMSO using NMR Varian-Mercury 300 MHz spectrometer. Chemical shifts are reported in δ ppm units with respect to Tetramethyl Silane as internal standard and coupling constants (*J*) were reported in Hz units. Mass spectra were obtained on an Electron Impact mass spectrometer at 70 eV ionizing beam using direct insertion probe.

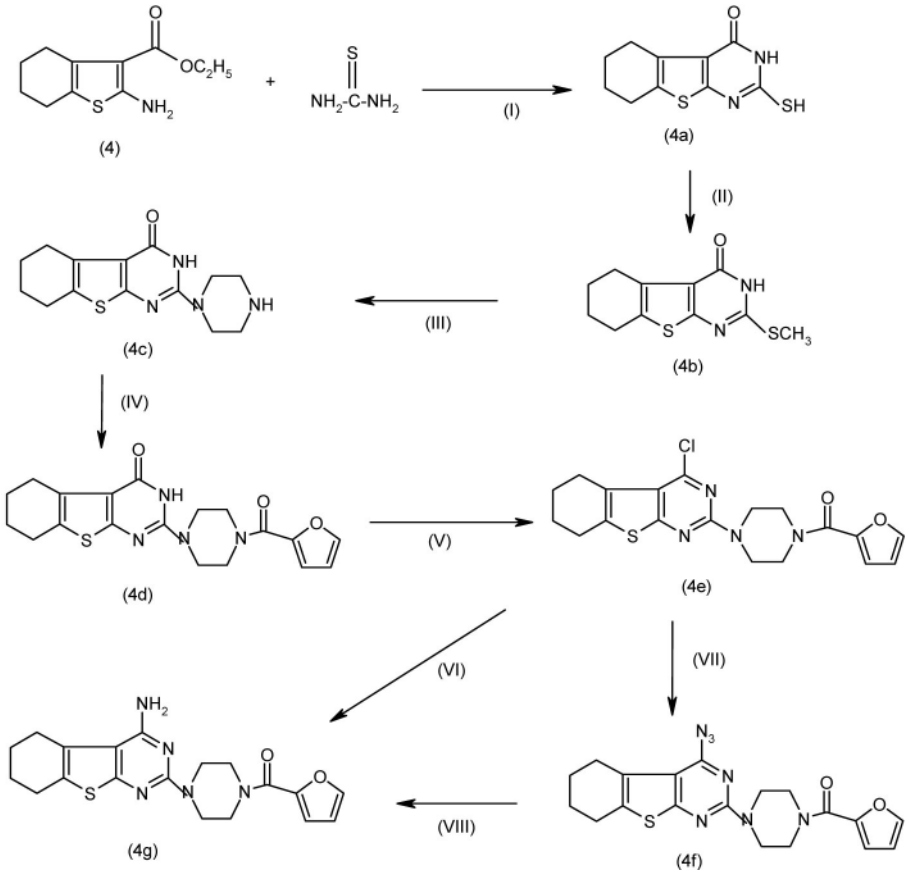
SYNTHESIS

The starting material 3,4-dimethoxybenzaldehyde[6] and Methyl-2-amino-4,5-dimethoxybenzoate (a) required for the synthesis of target compound was prepared by the reported method [4].

Synthesis of Bioisoster of Prazosin:

All prime starting materials required in the scheme II had been synthesized, and at this moment it was

Scheme III: Bioisosteric analog of Prazosin (I) NH_2CSNH_2, HCL(50%), MW; (II) dimethyl sulphate, NaOH (20%), 0-5°C, 3-4h; (III) unhydrous piperazine, isopropyl alcohol, MW; (IV) 2-furoyl chloride, isopropyl alcohol, potassium carbonate, TEBA chloride, MW; (V) $POCl_3$, isopropyl alcohol, MW; (VI) NH_3, THF, 0-5°C, 2h; (VII) NaN3, THF, 135-140°C; (VIII) Zn, AcOH, 95-105°C.



decided to setup reaction conditions of various steps involved in scheme II. Compared to directly trying the reactions with 4,5-dimethoxyanthranilonitrile or methyl-2-amino-4,5-dimethoxybenzoate which were rather not easily accessible because it can be only prepared by multistep syntheses, it was thought most of process development work could be done with more simple, inexpensive and easily accessible starting material. One such starting material, bioisoster of dimethoxy-methylanthranilate, was 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo-(*b*)-thiophene (4). It was prepared in a one-pot, single step process in excellent yield by utilizing Gewald reaction [7]. Thus, it was decided to adopt scheme III, involving use of thiophene-*o*-amino-ester as starting material, which bestow the thiophene analog of prazosin.

Synthesis of Prazosin bioisoster, 4-amino-2-[(4-(2-furoyl)-1-piperazinyl]-5,6,7,8-tetrahydrobenzo-(*b*)-thieno-(2-3*d*)-pyrimidine-4-(3*H*) (4f); Synthesis of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo-(b)-thiophene[7,8] (4):

A mixture of cyclohexanone (1 mol), sulfur (0.1 mol), ethylcyanoacetate (0.1 mol) and ethanol (20 ml) was stirred. To well stirred mixture diethylamine (0.125 mol) was added dropwise for half hour and stirring continued for another 3 hours at ambient temperature, once all sulfur got dissolved, reaction mixture was kept at 0-5°C for overnight. The solid separated was filtered next day, washed with 20 ml chilled 50% aqueous methanol. The product (75% yield) having mp 111-112°C (115°C) was characterized as 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo-(b)-thiophene.

Yield 75%, mp 111-112°C, IR (KBr) cm^{-1}: **3414, 3306, 3165, 3074, 2988, 1649.** *Anal.* Calcd for $C_{11}H_{15}NO_2S$.

Synthesis of 2-Mercapto-5,6,7,8-tetrahydrobenzo-(*b*)-thieno[2,3-*d*]pyrimidine-4-one (4a):

A mixture of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo-(*b*)-thiophene (0.004mole) and thiourea 0.008mole) were added to a round bottom flask and mixed well, to this mixture HCl (50%) was added till moist mass obtained. The mixture was irradiated with microwave (90 W) for 5 min, with cold shocks of half min. The reaction mixture was dissolved in 30ml sodium hydroxide solution (20% w/v) cooled to 0-5°C. The solution was acidified with conc. HCl producing white colored solid, washed with cold water, filtered out, and dried. The product (87% yield) having mp 212-214°C (213-215°C) was characterized as 2-mercapto-5,6,7,8-tetrahydrobenzo(*b*) thieno[2,3-d]pyrimidine-one(4a).

Yield 87%, mp 212-214°C, IR (KBr) cm^{-1}: **1802,** 1678, 1598, 669. *Anal.* Calcd for $C_{10}H_{10}N_2OS_2$

Synthesis of 2-thiomethyl-4-oxo-5,6,7,8-tetrahydrobenzo-(*b*)-thieno[2,3-*d*]pyrimidine (4b):

2-mercapto-5,6,7,8-tetrahydrobenzo-(*b*)-thieno[2,3-*d*]pyrimidin-4one (3a) (0.02mole) was dissolved in 20 ml sodium hydroxide solution (20% w/v), cooled to 0-5°C. In this solution dimethyl sulphate (0.04mole) was added dropwise for half hour with stirring. The reaction mixture was further stirred for another 2 h and kept at 0-5°C for overnight. The solid separated out was filtered, washed and dried. The product (67% yield) having m.p.235-237°C (310-311°C) was characterized as 2-thiomethyl-5,6,7,8-tetrahydrobenzo(*b*)thieno[2,3-*d*] pyrimidin-4-one(4b).

Yield 67%, mp 310-311°C, IR (KBr) cm^{-1}: 2985, 1722, 1657, 1597, 656. *Anal.* Calcd for $C_{11}H_{12}N_2OS_2$

Synthesis of 2-(N-piperazinyl)-5,6,7,8-tetrahydrobenzo(b)thieno[2,3-d]pyrimidin-4-one (4c):

A solution of 2-thiomethyl-4-oxo-5,6,7,8-tetrahydrobenzo(*b*)thieno[2,3-*d*]pyrimidine (0.012mole) and anhydrous piperazine (0.036mole) were mixed in a round bottom flask, fitted with a reflux condenser. This mixture was refluxed for 5-6 h. The reaction mixture was poured in ice-water (30ml) solid separated out was filtered washed and dried. The product (86% yield) having m.p.214-216°C was characterized as 2-(N-piperazinyl)-4-oxo-5,6,7,8-tetrahydrobenzo(*b*)thieno[2,3-*d*]pyrimidine (4c).

Yield 86%, mp 214-216°C, IR (KBr) cm^{-1}: 2958, 1705, 1679, 1685, 1556, 675. *Anal.* Calcd for $C_{14}H_{18}N_4OS$.

Synthesis of 2-[4-furoyl-(N-piperazinyl)]-4-oxo-5,6,7,8-tetrahydrobenzo(*b*)thieno-[2,3-*d*]-pyrimidine(4d):

A mixture of 2-(N-piperazinyl)-4-oxo-5,6,7,8-tetrahydrobenzo(*b*)thieno[2,3-*d*] pyrimidine (4c) (0.017 mol) and 2-furoyl chloride (0.034 mol) was prepared in N,N'-dimethylformamide (50ml) in a round bottom flask, then potassium carbonate

(0.034mole) and TEBA-chloride (0.001mole) were added. The resulting mixture was irradiated with microwave for 2-2.5 h. (90 W), then the reaction mixture was poured in ice cold water and the solid separated out was filtered and dried. The product (85% yield) having m.p.285-287°C was characterized as 2-[4-furoyl-(N-piperazinyl)]-4-oxo-5,6,7,8-tetrahydrobenzo(*b*) thieno[2,3-*d*]pyrimidine (4d).

Yield 85%, mp 285-287°C, IR (KBr) cm^{-1}: 2959, 1711, 1597, 1597, 1189, 1145, 679. *Anal.* Calcd for $C_{19}H_{20}N_4O_3S$.

Synthesis of 2-[4-furoyl-(N-piperazinyl)]-4-chloro-5,6,7,8-tetrahydrobenzo(*b*)thieno[2,3-*d*] pyrimidine(4e):

The 2-[4-furoyl-(N-piperazinyl)]-4-oxo-5,6,7,8-tetrahydrobenzo(*b*)thieno[2,3-*d*] pyrimidine (4d), (0.01mole) was dissolved in phosporous oxychloride (1.5 mol), in an iodine flask fitted with a reflux condenser and a guard tube. The reaction mixture was refluxed for 3-4 h. From the reaction mixture phosphorous oxychloride was distilled out at reduced pressure. Thereafter reaction mass was quenched in ice cold water, and upon neutralization with sodium bicarbonate, precipitate obtained. The product (76% yield) having m.p.178-181°C was characterized as 2-[4-furoyl-(N-piperazinyl)]-4-chloro-5,6,7,8-tetrahydrobenzo (*b*)thieno[2,3-*d*]pyrimidine (4e).

Yield 76%, mp 178-181°C, IR (KBr) cm^{-1}: 2898, 1781, 1581, 1601, 1139, 1074, 789. *Anal.* Calcd for $C_{19}H_{19}ClN_4O_2S$.

Synthesis of 2-[4-furoyl-(N-piperazinyl)]-4-amino-5,6,7,8-tetrahydrobenzo(*b*)thieno[2,3-*d*] pyrimidine (4g):

A solution of 2-[4-furoyl-(N-piperazinyl)]-4-chloro-5,6,7,8-tetrahydrobenzo(*b*)thieno[2,3-*d*] pyrimidine (0.001mole) was prepared in tetrahydrofuran (25 ml) in a round bottom flask, and cooled to 0-5°C. Dry ammonia gas was generated and passed through the solution of compound. A white colored precipitate was separated out, which was filtered out and dried. The product (68% yield) having mp 210-212°C was characterized as 2-[4-furoyl-(N-piperazinyl)]4-amino-5,6,7,8-tetrahydrobenzo (*b*) thieno[2,3-*d*]pyrimidine(4g).

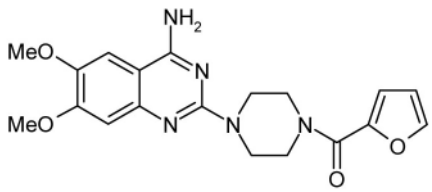
Yield 68%, mp 210-212°C, IR (KBr) cm^{-1}: 3504, 2898, 1781, 1581, 1601, 1139, 1074, 679.

^1H NMR (DMSO-*d*¬¬$_6$) δ: 2.6-2.7 (m, 2H, CH_2), 2.85 (m, 2H, CH_2), 3.1-3.3(m, 4H, CH_2), 3.7-4.1 (m, 8H, CH_2), 6.5 (broad s, 1H, CH_2), 7.0 (broad s 1H, CH), 7.3 (broad s, 1H, CH), 7.5 (s, 2H, NH_2). *Anal.* Calcd for $C_{19}H_{21}N_5O_2S$.

The final compound 2-[4-furoyl-(N-piperazinyl)] -4-amino-5,6,7,8-tetrahydrobenzo (*b*)thieno[2,3-*d*] pyrimidine can also be obtianed by the reaction of cholro compound (4e) with sodium azide (0.001 mol) in tetrahydrofuran (15 ml) at 135-140°C to produce azido intermediate (4f) with yield of 56%, and this can be further reduced with zinc (0.09 mol) in presence of acetic acid (10 ml) at 95-105°C to afford the final compound 2-[4-furoyl-(N-piperazinyl)]4-amino-5,6,7,8-tetrahydrobenzo(*b*)thieno[2,3-*d*]pyrimidine (4g) with 45% yield.

Synthesis of Prazosin:

Having synthesized principal starting material required for synthesis of prazosin and also successfully undertaken synthesis of its thieno-(2,3-*d*)-pyrimidine bioisosteric analog, the actual synthesis of prazosin was now taken up.



Prazosin

Synthesis of 2-mercapto-6,7-dimethoxyquinazolin-4-(3*H*)-one (b):

The methyl-2-amino-4,5-dimethoxybenzoate-(0.02mole) (2e), and thiourea (0.04mole), were mixed well and added HCL (50%) till wet mass obtained, in a round bottom flask. This mixture was irradiated with microwave for 5 min with shocks of 30 sec. The reaction mixture was dissolved in 30ml sodium hydroxide solution (20%), and filtered to remove any un-dissolved impurities, then cooled to 0-5°C, The solution was acidified with conc. hydrochloric acid; the greenish colored solid separated was filtered out, washed with ice-cold water, and dried. The product (77% yield) having m.p. 245-247°C was characterized as 2-mercapto-6,7-dimethoxyquinazolin-4-(3*H*)-one (b).

Yield 77%, mp 245-247°C, IR (KBr) cm^{-1}: 1756, 1702, 1678, 1596, 688. *Anal.* Calcd for $C_{10}H_{10}N_2O_3S$

Synthesis of 6,7-dimethoxy-2-(methylthio) quinazolin-4(3*H*)-one (c):

The 2-mercapto-6,7-dimethoxyquinazolin-4(3*H*) one (0.006mole) was dissolved in 20ml sodium hydroxide solution (20%), cooled to 0-5°C. To the above solution, dimethyl sulphate (0.018mol) was added drop wise for half an hour with stirring. Again it was stirred for another 2 h and placed in freezer for overnight. The solid separated out was filtered and dried. The product (84% yield) having m.p. 234-236°C was characterized as 2-thiomethyl-6,7-dimethoxyquinazolin-4(3*H*)one (c).

Yield 84%, mp 234-236°C, IR (KBr) cm^{-1}: 1747, 1713, 1667, 1597, 658. *Anal.* Calcd for $C_{10}H_{12}N_2O_3S$

Synthesis of 6,7-dimethoxy-2-piperazin-1-yl-quinazolin-4(3*H*)-one (d):

Solution of 2-thiomethyl-6,7-dimethoxyquinazolin-4(3*H*)one (0.003mole) and anhydrous piperazine (0.009mole) was dissolved in isopropyl alcohol in a round bottom flask fitted with a reflux condenser. This mixture was irradiated with microwave for 30-40min. The reaction mixture was quenched in ice-water (30ml); solid separated was filtered out, and dried. The product (82 % yield) having m.p. 325-327°C was characterized as 6,7-dimethoxy-2-piperazin-1-yl-quinazolin-4(3*H*)-one (d).

Yield 82%, mp 325-326°C, IR (KBr) cm^{-1}: 3514, 1757, 1711, 1597, 1597, 1189. Anal. Calcd for $C_{14}H_{18}N_4O_3$.

Synthesis of 4-furoyl-2-(piperazin-1-yl)-6,7-dimethoxyquinazolin-4(3H)one (e):

A mixture of 2-(piperazin-1-yl)-6,7-dimethoxy-quinazolin-4(3*H*)one (0.017 mol), and 2-furoyl chloride (0.04mol) was dissolved in isopropyl alcohol (30ml) in a round bottom flask, fitted with a reflux condenser. To this mixture potassium carbonate (0.03mol) and the PTC namely TEBA chloride in catalytic amount (0.001mole) was added. This mixture was irradiated with microwave (90W) (Intermittent cold cycles) for 30min. The reaction mixture was quenched in ice-water; solid separated was filtered and dried. The product obtained in 85% yield was characterized as 4-furoyl-2-(piperazin-1-yl)-6,7-dimethoxyquinazolin-4(3*H*)one(e). Thus, the crude product was recrystalised from methanol: chloroform (4:1) to afford the crystalline product having mp 278-280°C which was characterized by IR.

Yield 85%, mp 278-280°C, IR (KBr) cm^{-1}: 1757, 1711, 1597, 1597, 1189, 1145. Anal. Calcd for $C_{19}H_{20}N_4O_5$

Synthesis of 2-[4-furoyl-(piperazin-1-yl)]-4-chloro-6,7-dimethoxyquinazoline (f):

The 4-furoyl-2-(1-piperazinyl)-6,7-dimethoxyquinazolin-4-one (0.01mole) was dissolved in isopropyl alcohol (40ml), in an iodine flask fitted with a reflux condenser and guard tube. The reaction mixture was mixed with phosphorus-oxychloride (0.01mol) and refluxed for 8-9 hrs. The reaction mixture was quenched in ice-water and neutralized with sodium bicarbonate; the solid was filtered and dried. The product (78% yield) having m.p.175-178°C was characterized as 2-[4-furoyl-(1-piperazinyl)]-4-chloro-6,7-dimethoxyquinazoline (f).

Yield 78%, mp 175-176°C, IR (KBr) cm^{-1}: 1787, 1781, 1581, 1601, 1139, 1074, Anal. Calcd for $C_{19}H_{19}ClN_4O_4$

Synthesis of 2-[4-(2-furoyl)-piperazin-1-yl]-4-amino-6,7-dimethoxyquinazoline (h):

2-[4-furoyl-(piperazin-1-yl)]-4-chloro-6,7-dimethoxyquinazoline (0.009 mol) was dissolved in tetrahydrofuran in a round bottom flask, which was cooled at 0-5°C. The dry ammonia gas was generated from the gas generation assembly which was passed through the solution of 2-[4-furoyl-(piperazin-1-yl)]-4-chloro-6,7-dimethoxyquinazoline for about 2-3 h. The white colored product was separated out, which was filtered out, and dried. The product (70% yield) was characterized as 2-[4-(2-furoyl)-piperazin-1-yl]-4-amino-6,7-dimethoxy-quinazoline (g).

Yield 70%, mp 278-280°C, IR (KBr) cm^{-1}: 3504, 1650, 1580, 1528, 1465, 1287, 1000. ^1H NMR (DMSO-d_6) δ: 3.2-3.4 (m, 6H, CH_3), 3.6-4.1 (m, 8H, Piperazinyl), 6.4-6.45 (br. s, 1H, CH), 6.8-7.0 (br. s, 1H, CH), 7.8 (s, 1H, CH), 7.5-7.7 (m, 2H, Ar-H), 8.8 (s, 2H, NH_2). MS m/z: 383 (M^+), 288, 245, 233, 204. *Anal.* Calcd for $C_{19}H_{21}N_5O_4$.

The molecule 2-[4-(2-furoyl)-piperazin-1-yl]-4-amino-6,7-dimethoxy-quinazoline can also be obtianed by the reaction of cholro compound (f) with sodium azide (0.001 mol) in tetrahydrofuran (15 ml) at 145-150°C to produce azido intermediate (g) with yield of 46%, this can be further reduced with zinc (0.09 mol) in presence of acetic acid (10 ml) at 85-90°C to afford the final compound 2-[4-(2-furoyl)-piperazin-1-yl]-4-amino-6,7-dimethoxy-quinazoline (h) with 34% yield.

REFERENCES

1. De Smet PA. The role of plant-derived drugs and herbal medicines in healthcare. Drugs. 1997; 54(6): 801-40.
2. Brunton LL, Lazo JS, Parker KL. Eds. Goodman and Gilman's The Pharmacological basis of therapeutics. IX ed. USA. Mc Graw Hill medical publishing division; 1996: 780.
3. Manfred EW. Ed. Antihypertensive Agent, Burger's Medicinal Chemistry and Drug Discovery. Vol.2, Xth ed. Wiley-Interscience publication; 1996: 296-297.
4. Honkanen E, Pippuri A, Kairisalo P, et al. New practical synthesis of prazosin. J. Heterocycl. Chem. 1980; 17: 797-798.
5. Althius TS, Hess HJ. Synthesis and identification of the major metabolites of prazosin formed in dog and rat, J. Med. Chem. 1977; 20: 146-149.
6. Furniss BS, Hannaford AJ, Smith PWG, Et al. Vogel's textbook of practical organic chemistry, Vth ed. London. Pearson Prentice Hall Low price edition; 2004: 987.
7. Gewald K. Angew. Chem. 1961; 73: 114-118.
8. Gewald K. Chem. Ber. 1965; 98: 3571-3578.